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09/229,173	01/13/1999	DEB K. CHATTERJEE	0942.2800008	7438

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	37

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/229,173	Applicant(s) CHATTERJEE, DEB K.	
	Examiner Richard G Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-10,13,16,17,19,26,28,29,34-38 and 40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *38 and 40-44* is/are allowed.

6)☒ Claim(s) *1,3,5-10,13,16,17,19,26,28,29 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10, 28, 29*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment of claims 1, 9 and 37, Paper No. 31, 1/10/2003, is acknowledged. Claims 1, 3, 5-10, 13, 16, 17, 19, 26, 28, 29, 34-38, and 40-44 are still at issue and are present for examination.

Applicants' arguments filed on 1/10/2003, Paper No. 31, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

It is noted that the examiner has considered the document AP1 cited in the first supplemental Information Disclosure Statement filed on August 28, 2000 and has included an initialed copy of the corresponding 1449.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5-10, 13, 16, 17, 19, 26, 28, 29 and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 (3, 5-10, 13, 16, 17, 19, 26, 28, 29, 34-37 dependent from) were previously rejected as indefinite in that the metes and bounds of what applicants considers to be the "3'-5' exonuclease domain" and the "5'-3' exonuclease domain" of the claimed mutant *Thermotoga maritima* DNA polymerase mutants was unclear.

In response to this previous rejection, applicants argued that it is clear what "he" considers to the "3'-5' exonuclease domain" and the "5'-3' exonuclease domain". Applicants argued that the 3'-5' and 5'-3' exonuclease domains correspond to *Tma* DNA polymerase sequences that encode portions of the Tma DNA polymerase exhibiting 3'-5' exonuclease activity and 5'-3' exonuclease activity, respectively, and applicants refer to U.S. Patent No. 5,374,553 (which is incorporated by reference) which contains *Tma* DNA polymerase amino acid sequence. Thus applicants submit that the meets and bounds of the claims are clear.

Applicants previous argument is found persuasive in part, specifically with respect to the "3'-5' exonuclease domain", as Gelfand et al., U.S. Patent No. 5,374,553 (which is incorporated by reference) define the 3'-5' exonuclease domain of *Tma* DNA polymerase as represented by amino acids 291 through 484 (See column 7, lines 16-34 and column 13, lines 51-53). **Further it is suggested that applicants amend the instant specification to include this definition of the 3'-5' exonuclease domain of *Tma* DNA polymerase.**

However, neither Gelfand et al. nor applicants define the 5'-3' exonuclease domain of *Tma* DNA polymerase beyond being at the amino terminal of the *Tma* protein

and therefore the claims remain unclear in that the metes and bounds of what is considered to be encompassed by the 5'-3' exonuclease domain is unclear.

Claims 1, 3, 5-10, 13, 16, 17, 19, 26, 28, 29 and 34-37 are further indefinite in that the recitation "...wherein said mutation is selected from the group consisting of: a deletion, a single or double substitution, a point mutation, a frame shift mutation and an insertion" is unclear. It is unclear what the difference between a single substitution and a point mutation is and thus the inclusion of both of these types of mutations in the group of specific mutations sought is confusing. Further, the inclusion of frame shift mutations in the group of sought mutations is unclear as frame shift mutations would result in the not only the potential loss of 5'-3' exonuclease activity, 3-'5' exonuclease activity and discriminatory behavior against dideoxynucleotides, but the loss in polymerase activity itself, as presumably any domain which follows the frame shift, as one would read amino-terminal to carboxyl-terminal, would be lost. As the polymerase domain is on the carboxyl terminal side of each of the specifically referred to domains, any frameshift that would result in loss of exonuclease activity would also result in a loss in polymerase activity.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-8, 10, 13, 16, 17, 19, 26, 28, 29 and 34-37 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is stated in the previous office actions, Paper No. 12, 11/21/2000, Paper No. 15, 7/30/2001 and Paper No. 26, 5/1/2002 and applicants traversals are found in Paper No. 14, 5/21/2001, Paper No. 20, 12/18/2001, Paper No. 26, 5/1/2002 and Paper No. 31, 1/8/2003.

In response to the previous rejection, applicants have amended claims 1, 9 and 37. Claims 1 and 37 have been amended to recite that "said mutation is selected from the group consisting of: a deletion, a single or double substitution, a point mutation, a frame shift mutation and an insertion" and applicants traverse the rejection as it applies to the amended claims. While applicants have narrowed the scope of the claimed Tma DNA polymerase mutants, the amended claims remain rejected.

The rejected claims are now directed to all possible *Thermotoga maritima* (*Tma*) DNA polymerase mutants which are modified at least two ways selected from the group consisting of (a) a mutation in the 3'-5' exonuclease domain of said polymerase to reduce or eliminate the 3' 5' exonuclease activity of the polymerase; (b) a mutation in the 5'-3' exonuclease domain of said polymerase to reduce or eliminate the 5'-3' exonuclease activity of the polymerase; and (c) a mutation in the O-helix of said polymerase to reduce or eliminate discriminatory behavior against a dideoxynucleotide

wherein said mutation is selected from the group consisting of: a deletion, a single or double substitution, a point mutation, a frame shift mutation and an insertion, and methods of using and kits comprising said DNA polymerase mutants and genes encoding said DNA polymerase mutants

Applicants continue to traverse this rejection on the basis that the test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed and applicants submit that the specification of the captioned application provides sufficient description of Tma DNA polymerase mutants, strong evidence of a function/structure relationship and adequate description of representative species. Applicants submit that the level of skill and knowledge in the art at the priority date of the present application was substantial, and that the claimed Tma DNA polymerase belongs to the Pol I-type family of DNA polymerases and that the specification teaches that the *Thermotoga* DNA polymerase of the invention can be isolated from any strain of *Thermotoga* which produces a DNA polymerase. Applicants arguments are noted and applicant is reminded that while knowledge of the art is relevant to the adequate written description of a claimed genus, the current rejection is not based on a lack scope of enablement. As such while the level of skill in the art and knowledge at the priority date of the present application was substantial, such that the claimed genus was enabled, the claimed genus was not described, such that given the knowledge in the art and the teachings of the specification, including the taught representative species, one could not predict the many additional species of the claimed genus. This is based on the fact that

applicants have not taught the structure to function/activity relationship of the claimed genus. The specification only provides a Tne DNA polymerase mutant consisting of a combination of the following mutations: those mutants having reduced 3'-5' exonuclease activity consisting of Asp^{323} converted to Ala^{323}, those mutants having reduced discriminatory behavior against a dideoxynucleotides, consisting of Phe^{730} converted to Tyr^{730} and those mutants having reduced 5' 3' exonuclease activity consisting of the deletion of 219 amino terminal amino acids of Tne DNA Polymerase and Asp^{8} converted to Ala^{8} or Asp^{137} converted to Ala^{137} (Examples 11-13 and 16). For example, applicants argue that the 3'-5' exonuclease domain of *Tma* DNA polymerase is represented by amino acids 291 through 484. Applicants have taught a single Asp^{323} converted to Ala^{323} mutation of this domain, which is over 100 amino acids, wherein said mutation has the claimed reduction in 3'-5' exonuclease activity. This species is not representative of the genus of DNA polymerases in which the polymerase is modified selected from the group consisting of: a deletion, a single or double substitution, a point mutation, a frame shift mutation and an insertion. Applicants have not taught how such structural changes of the claimed DNA polymerases relate to the 3'-5' exonuclease activity of the polymerase nor are those modifications within this group which will result in the claimed functional changes predictable.

The identification of conserved regions and consensus sequence motifs, while helping applicants describe those regions in which the claimed mutations should be made beyond say the identification of the 3'-5' exonuclease, 5'-3' exonuclease domain or the O-helix, does not provide sufficient description of the specific amino acid

modifications selected from the group consisting of a deletion, a single or double substitution, a point mutation, a frame shift mutation and an insertion that will result in the claimed functional modifications. The mere identification of conserved amino acid residues associated with an activity such as 5'-3' exonuclease activity does not adequately describe those mutations of the 5'-3' domain selected from the group consisting of: a deletion, a single or double substitution, a point mutation, a frame shift mutation and an insertion that will result in the claimed functional modifications.

Applicants argue that based on the state of the art, homology between different Pol I-type DNA polymerizes, identification of conserved residues in conserved domains and specific mutants identified by the art, applicants have provided guidance to one skilled in the art to envision numerous specific mutations in addition to those described in the specification, that will reduce or eliminate 3'-5' and 5'-3' exonuclease activity. While applicants have adequate description beyond those specific mutations taught by the specification, applicants have not adequately described all possible *Thermotoga maritima* (*Tma*) DNA polymerase mutants which are modified at least two ways selected from the group consisting of (a) a mutation in the 3'-5' exonuclease domain of said polymerase to reduce or eliminate the 3' 5' exonuclease activity of the polymerase; (b) a mutation in the 5'-3' exonuclease domain of said polymerase to reduce or eliminate the 5'-3' exonuclease activity of the polymerase; and (c) a mutation in the O-helix of said polymerase to reduce or eliminate discriminatory behavior against a dideoxynucleotide wherein said mutation is selected from the group consisting of: a deletion, a single or double substitution, a point mutation, a frame shift mutation and an insertion.

It is acknowledged that that there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. It is further acknowledged that as applicants submit 1) there is detailed and well known structural information for DNA polymerizes; 2) structure/function correlations are available for these DNA polymerizes; and 3) the sequence and other structural information for the Tma DNA polymerizes are provided. However the structure/function correlations available for the DNA polymerizes are not sufficient to adequately predict the genus of polymerizes claimed comprising all possible *Thermotoga maritima* (*Tma*) DNA polymerase mutants which are modified at least two ways in the specified domains selected from the group consisting of a deletion, a single or double substitution, a point mutation, a frame shift mutation and an insertion. Applicants have especially not described any mutants selected from the group consisting of frameshift mutations and insertions.

As previously stated, the claimed genus includes all possible *Thermotoga maritima* (*Tma*) DNA polymerase mutants which are modified at least two ways selected from the group consisting of (a) a mutation in the 3'-5' exonuclease domain of said polymerase to reduce or eliminate the 3'-5' exonuclease activity of the polymerase; (b) a mutation in the 5'-3' exonuclease domain of said polymerase to reduce or eliminate the 5'-3' exonuclease activity of the polymerase; and (c) a mutation in the O-helix of said polymerase to reduce or eliminate discriminatory behavior against a dideoxynucleotide, including any mutation of said domains including amino acid substitutions, deletions and insertions of single as well as multiple amino acids, point mutations, (frame shift

mutations (See also above 112 2nd paragraph rejection). As stated in the previously, there is no disclosure of any particular structure to function/activity relationship in the claimed genus. While the specification provides the species, $Asp^{323} \rightarrow Ala^{323}$, (having reduced 3'-5' exonuclease activity), $Phe^{730} \rightarrow Tyr^{730}$ (having reduced discriminatory behavior against a dideoxynucleotides) and $Asp^{8} \rightarrow Ala^{8}$, $Asp^{137} \rightarrow Ala^{137}$ or the deletion of 219 amino terminal amino acids of Tne DNA Polymerase (having reduced 5'-3' exonuclease activity) encompassed by these claims, the specification clearly does not disclose a representative number of species of the claimed genus which includes an **infinite number of amino acid variants** of any *Tma* DNA polymerases. Even considering the substantial knowledge of the skilled artisan, as detailed by applicants, one could only envision a small number of additional species within the scope of the claimed genus. However, in view of the enormous breadth of the claimed genus, even these could in no way be considered to be representative of the entire genus. There is no disclosure of any particular structure to function/activity relationship in the claimed genus. The disclosed species of mutant *Tma* DNA polymerases and others described in the art all have **minor** structural limitations such that the infinite number of species encompassed by this genus have not been adequately described by the few species disclosed in the specification.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
April 4, 2003